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L. EDELEN
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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

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INVENTOR(S)/APPLICANT(S)			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Hylands	Peter		Worcestershire, United Kingdom

TITLE OF THE INVENTION (280 characters)

PROCESS FOR QUALITY CONTROL OF MEDICINAL PLANT PRODUCTS

CORRESPONDENCE ADDRESS

Arthur R. Crawford
NIXON & VANDERHYE P.C.
1100 North Glebe Road
8th Floor
Arlington

STATE	Virginia	ZIP CODE	22201	COUNTRY	U.S.A.

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Respectfully submitted,
SIGNATURE _____ DATE February 18, 1999

TYPED or PRINTED NAME **Arthur R. Crawford** REGISTRATION NO. *(if appropriate)* **25,327**

[ ] Additional inventors are being named on separately numbered sheets attached hereto.

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SPECIFICATION

FOR

PATENT APPLICATION

IN

UNITED STATES OF AMERICA

in the name of *Dr Peter Hylands* of *Laundry Cottage, Yewleigh Lane, Upton-upon-Severn, Worcestershire WR8 0QW, United Kingdom*

PROCESS FOR QUALITY CONTROL OF MEDICINAL PLANT PRODUCTS

The present invention relates to the quality control of medicinal and nutritional substances derived from plants. In particular the invention relates to a process for producing a plant based medicinal or nutritional substance which satisfies a pre-defined pharmaceutical grade standard and which can therefore be licensed by drug regulatory authorities as a pharmaceutical product. The invention also allows the origin or quality of a plant based material to be determined by comparison with a standard, thereby providing a means for the standardisation, quality control, tracking and audit of such materials.

Many societies around the world have developed, through the centuries, a system of traditional medicine relying largely on the use of plants and herbs as therapeutic substances. Studies into the structures of the isolated active ingredients of these substances led to the chemical phase of drug discovery in the early and middle twentieth century. As a result some important drugs were developed which owe their origin to the empirical use of plants in traditional medicine.

In recent years there has been a significant growth of interest amongst the general public in the direct use of plants and plant extracts as health modifying agents, for instance ginseng, garlic, *Ginkgo biloba*, *Hypericum* (St John's wort), *Echinacea* and *Aloe Vera*. These are currently available on the market as herbal products and dietary supplements and annual sales of these products worldwide are currently in excess of £10 billion. In spite of this marketing potential the mainstream pharmaceutical industry has not so far directed its attention to the development of medicinal products derived from plants. This is due in part to problems associated with the complex nature and inherent non-uniformity of plant materials, including the lack of an established system by which drug regulatory approval for such products can be secured.

The materials used in herbal and plant based medicine are usually whole plants, parts of plants or plant extracts. Since plant materials contain many different

chemical components the materials are, by definition, complex mixtures. This makes it very difficult to standardize and control the quality of the materials. Furthermore, plants used in the practice of herbal medicine are frequently unavailable locally and therefore need to be obtained from sources which are remote from the end user. However, the supply of such plants from remote locations can be erratic and inaccurate, particularly because no detailed monographs (identity and quality standards) exist for the plants. The complex mixture of ingredients found in medicinal plants will in any event vary widely in type and concentration depending on many factors including the botanical origin, the location where the plant is grown, the time or year when the plant is harvested and the extraction procedure used.

As a consequence it is virtually impossible to provide any assurance that samples of a given plant material obtained from disparate sources will possess a uniform identity and biological activity. This inherent variability of plant materials presents a problem to the drug regulatory authorities who need to be convinced that a candidate product for pharmaceutical licencing is of a consistent and verifiable quality. This is so that, for instance, the effectiveness of dosage levels and treatment protocols can be guaranteed. However, there is no reliable system available at present which both allows the identity and activity of a plant based product to be measured against an accepted standard and is universally applicable to all kinds of plant material.

The present invention addresses this problem and, in one aspect, provides a process for producing a pharmaceutical grade therapeutic substance which is derived from, or consists of, a plant material, the process comprising:

(i) providing a test sample of the therapeutic substance in the form of a solution or extract;

(ii) submitting the test sample to two or more test methods selected from a panel of chemical analytical and biological profiling techniques, the selected test methods including at least one chemical analytical technique and at least one biological profiling technique;

(iii) determining whether the test sample provides, in each of the methods

selected in step (ii), test results which match those of a pre-determined pharmaceutical quality standard sample; and

(iv) selecting the therapeutic substance as being of pharmaceutical grade only if the test results all match those of the said standard sample.

The invention thus resides in the provision of an array of chemical and biological analytical techniques which, in combination, enable a plant derived substance to be uniquely characterised. The substance can then be accepted or rejected depending on whether its characterisation matches that of a pre-determined pharmaceutical grade standard.

The particular combination of test methods used for a given plant substance will need to be selected on a case-by-case basis, It includes at least one chemical analytical technique and at least one biological profiling technique since, in general, a description of a plant material based on chemistry alone is likely to be inadequate. A means of quality controlling each sample in terms of its biological activity is therefore required in addition to chemical characterisation. This is because the complex mixture of compounds in the material may show an overall clinical effect which derives principally from one particular component but which is considerably modified or potentiated by the presence of other components. Biological profiling can thus provide a quantifiable measure of the biological effects of plants and plant extracts, thereby complementing the information obtained by chemical analysis.

In a preferred aspect of the invention the chemical analytical techniques in the panel include high resolution NMR fingerprinting and chromatographic analysis. In another preferred aspect the biological profiling techniques in the panel include a receptor binding or enzyme inhibition assay, signal transduction analysis and protein analysis. In a particularly preferred aspect of the invention the panel of chemical, analytical and biological profiling techniques consists of high resolution NMR fingerprinting, chromatographic analysis, a receptor binding or enzyme inhibition assay, signal transduction analysis and protein analysis.

The high resolution NMR fingerprinting technique typically comprises:

(i) submitting the test sample to high field proton NMR and recording one or more NMR spectra;

(ii) evaluating the data obtained from the or each NMR spectrum by one or more computer-based pattern recognition procedures to obtain an NMR fingerprint of the sample; and

(iii) determining the presence or absence of marker features in the fingerprint which have been previously identified in the NMR fingerprint of a pharmaceutical quality standard sample.

The high resolution NMR fingerprinting technique thus involves a combination of ^{1}H NMR at high fields and computer based pattern recognition procedures. The NMR spectra are typically measured at 400 to 700 MHz, and the data derived from them are analysed by computer programs using techniques such as non-linear mapping and principal component analysis. Examples of the high resolution NMR fingerprinting technique are discussed by M. L. Anthony *et al* in Biomarkers 1996, 1, 35- 43 and Molecular Pharmacology 46, 199- 211, 1994, and by J.O.T. Gibb *et al* in Comp. Biochem. Physiol. vol. 118B No. 3, pp 587- 598, 1997.

An important advantage of this NMR technique is that it is not limited by a selective delivery or detection system. Spectra are recorded without prior purification of the test sample, thus allowing all components of the sample to contribute to the overall NMR "fingerprint". Analysis by the pattern recognition procedures as discussed above reveals potential valuable marker features of the spectra which can be used with a high degree of precision in the characterisation of the complex mixtures of components contained in plant materials.

The chromatographic analysis preferably involves conventional high performance liquid chromatography (HPLC) and is typically combined with solid phase extraction. A preferred technique of chromatographic analysis comprises carrying out a sequence of serial and parallel chromatographic separations to fractionate the test sample, and comparing the fractionation profile thus obtained with the fractionation profile previously obtained from a pharmaceutical quality standard sample. This particular method is well suited to automation and quantification, and is thus well suited to the drug regulatory aspect of the present invention.

The biological profiling techniques used in the process of the invention

provide a means of quality controlling a given sample of plant material in terms of its biological activity. It is possible by this means to identify the principal components of a plant material which give rise to a particular therapeutic effect exerted by the material. However, it is now recognised that the overall efficacy of plant based medicines does not solely derive from a single active component but is due also to auxiliary compounds which are present in the complex mixture of substances in the plant. The biological profiling techniques used in the process of the invention allow synergistic effects exerted by these auxiliary compounds to be studied. The synergistic effects which may be observed include, for instance, potentiation of the activity of the principal component, enhancement of the selectivity or bioavailability of the therapeutic substance and suppression of unwanted side effects. This aspect of the biological profiling is particularly useful for substantiating the claim that the use of a whole plant or plant extract in therapy is more beneficial than the use of single components isolated from the plant.

One of the preferred biological profiling techniques is a signal transduction analysis, which typically comprises:

(i) providing a target cell selected according to the clinical indication in which the therapeutic substance is active;

(ii) incubating the target cell with the test sample, disposing the incubated cells on a gel and separating the constituent proteins by gel electrophoresis;

(iii) subjecting the separated proteins to immunoblotting so as to visualise the extent of change in the phosphorylation status of proteins in the target cell as a result of exposure to the test sample; and

(iv) comparing the pattern of bands on the gel resulting from step (ii) with the pattern obtained previously from a pharmaceutical quality standard sample.

In the first step of this analysis an appropriate target cell is selected according to the clinical indication or disease, which it is desired to model. In the second step the cells are incubated with the test sample, typically in increasing concentrations, dissolved in a general solvent. A suitable solvent would be dimethylsulfoxide

(DMSO). Following the incubation period, which may be from several hours to several days, the cells are harvested and prepared for visualization in the third step.

In preparation for the visualization in step (iii) of signal transduction pathways affected by the exposure of the target cells to the test sample, the harvested cells are lysed and the proteins in the lysate are separated by gel electrophoresis. This is preferably by means of a process termed 2-dimensional, or 2-D, SDS-PAGE (sodium dodecyl sulphate polyacrylamide gel electrophoresis). The separated proteins are then transferred from the gel to a membrane. The membrane is typically blocked with saline buffered with Tris (tris(hydroxymethyl)aminomethane) containing 5% commercial non-fat dry milk. Tyrosylphosphorylation of cellular proteins can then be visualized in the immunoblotting step (iii) using an antibody for phosphotyrosine and an antibody of IgG with an alkaline phosphatase enzyme linkage. Similarly, serine or threonine phosphorylation of total cellular proteins can be visualised with anti-phosphoserine and anti-phosphothreonine antibodies, respectively.

A resulting pattern of bands is obtained on the gel, thereby providing a characteristic fingerprint for each signalling pathway. The pattern indicates the extent of change in the phosphorylation status of various proteins in the cell as a result of exposure to the extract of the test sample. The potency of the test sample can then be related to the potency of a pharmaceutical grade standard by comparing the concentration of the test sample necessary to produce the response of the standard. The signal transduction analysis technique thus permits the quality control of a test sample of plant material without knowledge of any details of the mechanism of biological action of the material.

Another preferred biological profiling technique is protein analysis, which typically comprises:

(i) providing a target cell selected according to the clinical indication in which the therapeutic substance is active and incubating the target cells with the test sample;

(ii) subjecting the incubated cells to gel electrophoresis on a 2-D gel and observing the change in protein expression in the cells as a result of

exposure to the test sample; and

(iii) comparing the overall pattern of change in protein expression observed in step (ii) with the corresponding pattern of change brought about by incubation of the test cell with a pharmaceutical quality standard sample

An appropriate target cell is selected in the first step according to the clinical indication, or disease, which it is desired to model. Following incubation of the cell with the test sample, the proteins in the plant material are separated into individual proteins by two dimensional electrophoresis. Detection and analysis of the resulting protein patterns is typically undertaken using computerized image analysis techniques, and proteins are identified using microsequencing and mass spectroscopy. Changes in protein expression which are detected following incubation of the target cell with the test sample are then compared with the corresponding changes detected following incubation of the target cell with a previously tested pharmaceutical quality standard sample.

A further preferred biological profiling technique is a receptor binding or enzyme inhibition assay. This can give a quantifiable measure of the biological activity of a plant material. Such an assay may be conducted in accordance with a conventional assay protocol. One example of a suitable assay is a method for screening a plant material as a candidate for the treatment or prophylaxis of cancer or inflammation, the method comprising determining whether the substance suppresses the stimulation of a gene promoter which has been implicated in carcinogenesis or inflammation.

In the process of the invention the therapeutic substance typically consists of, or is derived from, a whole plant, a part of a plant, a plant extract or a plant fraction. Preferably the substance consists of, or is derived from, one or more of the roots, leaves, buds, flowers, fruit, juice and seeds of a plant.

The process of the invention as described above relies upon the prior establishment of a pharmaceutical grade quality standard for the therapeutic substance in question, which is submitted to the panel of chemical analytical and biological profiling techniques to yield a set of standard test results. The

pharmaceutical grade quality standard for a therapeutic substance which is derived from, or consists of, a plant material may therefore be provided by a process comprising:

(i) providing a test sample of the therapeutic substance, of the quality desired for the standard, in the form of a solution or extract;

(ii) submitting the test sample to two or more test methods selected from a panel of chemical analytical and biological profiling techniques, the selected test methods including at least one chemical analytical technique and at least one biological profiling technique;

(iii) obtaining analytical results and biological profiles for the test sample in each of the test methods selected in step (ii); and

(iv) defining the combination of results and profiles obtained in step (iii) as the standard to be met by any sample of the substance which is to be recognised as being of the desired pharmaceutical grade quality.

In another aspect the present invention further provides a process for determining whether a nutritional or therapeutic substance which derives from, or consists of, a plant material, has a specified origin or a desired quality, the process comprising:

(i) providing a test sample of the substance in the form of a solution or extract;

(ii) submitting the test sample to two or more test methods selected from a panel of chemical analytical and biological profiling techniques, the selected test methods including at least one chemical analytical technique and at least one biological profiling technique;

(iii) determining whether the test sample provides, in each of the methods selected in step (ii), test results which match those of a previously tested standard sample having the specified origin or desired quality in question; and

(iv) selecting the substance as being of the specified origin or desired quality only if the test results all match those of the said standard sample.

In this process the chemical analytical and biological profiling techniques used are preferably selected from those described above in connection with the process for producing a pharmaceutical grade substance.

CLAIMS

1. A process for producing a pharmaceutical grade therapeutic substance which is derived from, or consists of, a plant material, said process comprising the steps of:

   (i) providing a test sample of the therapeutic substance in the form of a solution or extract;

   (ii) submitting said test sample to two or more test methods selected from a panel of chemical analytical techniques and biological profiling techniques, the said selected test methods including at least one chemical analytical technique and at least one biological profiling technique;

   (iii) determining whether said test sample provides, in each of said selected test methods in step (ii), test results which match those of a pre-determined pharmaceutical quality standard sample; and

   (iv) selecting said therapeutic substance as being of pharmaceutical grade only if said test results all match those of said standard sample.

2. A process according to claim 1 wherein said chemical analytical techniques are selected from the group consisting of high resolution NMR fingerprinting and chromatographic analysis.

3. A process according to claim 1 wherein said biological profiling techniques are selected from the group consisting of a receptor binding assay, an enzyme inhibition assay, signal transduction analysis and protein analysis.

4. A process according to claim 1 wherein said panel of chemical analytical and biological profiling techniques consists of high resolution NMR fingerprinting, chromatographic analysis, a receptor binding assay, an enzyme inhibition assay, signal transduction analysis and protein analysis.

5. A process according to claim 2 or 4 wherein said high resolution NMR fingerprinting technique comprises the steps of:

(i) submitting said test sample to high field proton NMR and recording one or more NMR spectra;

(ii) evaluating the data obtained from the or each said NMR spectrum by one or more computer-based pattern recognition procedures to obtain an NMR fingerprint of the sample; and

(iii) determining the presence or absence in said NMR fingerprint of marker features which have been previously identified in a corresponding NMR fingerprint of a pharmaceutical quality standard sample.

6. A process according to claim 5 wherein said computer-based pattern recognition procedures are selected from the group consisting of non-linear mapping, principal component analysis and cluster analysis.

7. A process according to claim 2 wherein said chromatographic analysis technique comprises carrying out a sequence of serial and parallel chromatographic separations to fractionate said test sample and generate a fractionation profile, and comparing said fractionation profile with a corresponding fractionation profile previously obtained from a pharmaceutical quality standard sample.

8. A process according to claim 3 wherein said biological profiling techniques are selected from the group consisting of signal transduction analysis, protein analysis, a receptor binding assay and an enzyme inhibition assay.

9. A process according to claim 8 wherein said signal transduction analysis comprises the steps of:

(i) providing a target cell selected according to the clinical indication in

which said therapeutic substance is active;

(ii) incubating said target cell with said test sample, disposing said incubated cells on a gel and subjecting said cells to gel electrophoresis so that the constituent proteins of said cells are separated;

(iii) subjecting said separated proteins to immunoblotting so as to generate a pattern of bands on said gel which indicates the extent of change in the phosphorylation status of proteins in said target cell as a result of exposure to said test sample; and

(iv) comparing said pattern of bands with a corresponding pattern obtained previously from a pharmaceutical quality standard sample.

10. A process according to claim 8 wherein said protein analysis comprises the steps of:

(i) providing a target cell selected according to the clinical indication in which the therapeutic substance is active and incubating said target cell with said test sample;

(ii) subjecting said incubated test cells to gel electrophoresis on a 2-D gel and observing the pattern of change in protein expression in said cells as a result of exposure to said test sample; and

(iii) comparing said pattern of change in protein expression with a corresponding pattern of change brought about by incubation of said test cell with a pharmaceutical quality standard sample

11. A process according to claim 1 wherein said therapeutic substance consists of, or is derived from, a member of the group consisting of a whole plant, a part of a plant, a plant extract and a plant fraction.

12. A process according to claim 1 wherein the therapeutic substance consists of, or is derived from, a member of the group consisting of the roots, leaves, buds, flowers, fruit, juice and seeds of a plant.

13. A process for determining whether a nutritional or therapeutic substance which derives from, or consists of, a plant material, has a specified origin or a desired quality, said process comprising the steps of:

(i) providing a test sample of said substance in the form of a solution or extract;

(ii) submitting said test sample to two or more test methods selected from a panel of chemical analytical techniques and biological profiling techniques, the said selected test methods including at least one chemical analytical technique and at least one biological profiling technique;

(iii) determining whether said test sample provides, in each of said selected test methods in step (ii), test results which match those of a previously tested standard sample having said specified origin or desired quality; and

(iv) selecting the substance as being of said specified origin or desired quality only if said test results all match those of said standard sample.

14. A process according to claim 13 wherein said chemical analytical techniques are selected from the group consisting of high resolution NMR fingerprinting and chromatographic analysis.

15. A process according to claim 13 wherein said biological profiling techniques are selected from the group consisting of a receptor binding assay, an enzyme inhibition assay, signal transduction analysis and protein analysis.

16. A process according to claim 13 wherein said panel of chemical analytical and biological profiling techniques consists of high resolution NMR fingerprinting, chromatographic analysis, a receptor binding assay, an enzyme inhibition assay, signal transduction analysis and protein expression analysis.

17. A process according to claim 14 wherein said high resolution NMR fingerprinting technique comprises the steps of:

(i) submitting said test sample to high field proton NMR and recording one or more NMR spectra;

(ii) evaluating the data obtained from the or each said NMR spectrum by one or more computer-based pattern recognition procedures to obtain an NMR fingerprint of said sample; and

(iii) determining the presence or absence in said NMR fingerprint of marker features which have been previously identified in a corresponding NMR fingerprint of said standard sample.

18. A process according to claim 17 wherein said computer-based pattern recognition procedures are selected from the group consisting of non-linear mapping, principal component analysis and cluster analysis.

19. A process according to claim 14 wherein said chromatographic analysis technique comprises carrying out a sequence of serial and parallel chromatographic separations to fractionate said test sample and generate a fractionation profile, and comparing said fractionation profile with a corresponding fractionation profile previously obtained from said standard sample.

20. A process according to claim 15 wherein said biological profiling techniques are selected from the group consisting of signal transduction analysis, protein analysis, a receptor binding assay and an enzyme inhibition assay.

21. A process according to claim 20 wherein said signal transduction analysis comprises the steps of:

(i) providing a target cell selected according to the clinical indication or biochemical mechanism in which said substance is active;

(ii) incubating said target cell with said test sample, disposing said

incubated cells on a gel and subjecting said cells to gel electrophoresis so that the constituent proteins of said cells are separated;

(iii) subjecting said separated proteins to immunoblotting so as to generate a pattern of bands on said gel which indicates the extent of change in the phosphorylation status of proteins in said target cell as a result of exposure to said test sample ; and

(iv) comparing said pattern of bands with a corresponding pattern obtained previously from said standard sample.

22. A process according to claim 20 wherein said protein analysis comprises the steps of:

(i) providing a target cell selected according to the clinical indication or biochemical mechanism in which said substance is active and incubating said target cells with said test sample;

(ii) subjecting said incubated test cells to gel electrophoresis on a 2-D gel and observing the pattern of change in protein expression in said cells as a result of exposure to said test sample; and

(v) comparing said pattern of change in protein expression with a corresponding pattern of change brought about by incubation of said test cell with said standard sample.

23. A process according to claim 13 wherein said nutritional or therapeutic substance consists of, or is derived from, a member selected from the group consisting of a whole plant, a part of a plant, a plant extract and a plant fraction.

24. A process according to claim 13 wherein said therapeutic substance consists of, or is derived from, a member selected from the group consisting of the roots, leaves, buds, flowers, fruit, juice and seeds of a plant.

25. A process for providing a pharmaceutical grade quality standard for a

therapeutic substance which is derived from, or consists of, a plant material, said process comprising the steps of:

(i) providing a test sample of said therapeutic substance, of the quality desired for said standard, in the form of a solution or extract;

(ii) submitting said test sample to two or more test methods selected from a panel of chemical analytical techniques and biological profiling techniques, said selected test methods including at least one chemical analytical technique and at least one biological profiling technique;

(iii) obtaining analytical results and biological profiles for said test sample in each of said test methods selected in step (ii); and

(iv) defining the combination of results and profiles obtained in step (iii) as the standard to be met by any sample of the substance which is to be recognised as being of the desired pharmaceutical grade quality.

ABSTRACT OF THE DISCLOSURE

A process for producing a pharmaceutical grade therapeutic substance which is derived from, or consists of, a plant material, comprises the steps of:

(i) providing a test sample of the therapeutic substance in the form of a solution or extract;

(ii) submitting said test sample to two or more test methods selected from a panel of chemical analytical techniques and biological profiling techniques, the said selected test methods including at least one chemical analytical technique and at least one biological profiling technique;

(iii) determining whether said test sample provides, in each of said selected test methods in step (ii), test results which match those of a pre-determined pharmaceutical quality standard sample; and

(iv) selecting said therapeutic substance as being of pharmaceutical grade only if said test results all match those of said standard sample.

The invention thus provides a means for the quality control of medicinal plant products and thereby overcomes problems associated with the inherently complex nature and variable quality of plant materials.